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**Neonatal intestinal failure is independently associated with impaired  
cognitive development later in childhood**

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## **Abstract**

**Objective:** The impact of pediatric intestinal failure (IF) on neurodevelopment beyond infancy has not been systematically studied. Our aim was to evaluate cognitive and motor impairment and to identify risk factors for adverse outcomes among children with IF.

**Methods:** We conducted a cross-sectional single-center study at the Helsinki University Children's Hospital. IF patients with > 60 days of parental nutrition (PN) dependency aged between three and sixteen years (n=40) were invited to participate. The cognitive and motor skills were evaluated using validated tests: Wechsler Preschool and Primary Scale of Intelligence, 3<sup>rd</sup> edition, Wechsler Intelligence Scale for Children, 4<sup>th</sup> edition, and Movement Assessment Battery for Children, 2<sup>nd</sup> edition.

**Results:** All the patients attending the study tests (n=30, males=24) were included. Their median age, gestational age and birth weight was 7.5 (range 3 to 16) years, 35 (IQR 28–38) weeks and 2,238 (IQR 1,040-3,288) grams, respectively. Median duration of PN was 13 (IQR 5-37) months and 9 patients were currently on PN. Median Intelligence quotient (IQ) was 78 (IQR 65–91) and ten (35%) patients had an IQ under 70 (-2 SD). Significant motor impairment was detected in 10 patients (36%) and milder difficulties in 8 (28%). Adverse cognitive outcome was associated with neonatal short bowel syndrome, number of interventions under general anesthesia, and length of inpatient status, while adverse motor outcome was associated with prematurity.

**Conclusion:** Clinically significant cognitive and motor impairments are alarmingly common among neonatal IF patients. We recommend early neurodevelopmental follow-up for all children with IF.

**Keywords:** Neurological Development; Neonatal Surgery; Parenteral Nutrition; Intelligence quotient; Short Bowel Syndrome

### **What is known on this subject?**

- During the neonatal period, intestinal failure (IF) patients are subject to various risk factors for adverse neurodevelopment.
- Previous studies have shown mild to moderate cognitive and motor impairment in this patient group during the first years of life.

### **What is new**

- We investigated the cognitive and motor function of pediatric IF patients after infancy. Adverse outcomes in cognitive and motor development were common.
- Cognitive impairment was associated with neonatal short bowel syndrome, the number of laparotomies and anesthesia and the length of hospitalization.
- We recommend standardized neurodevelopmental follow-up for children with history of IF.

## Introduction

Pediatric intestinal failure (IF) is defined as the reduction of functional gut mass under the level that is required to maintain normal growth and fulfil daily energy and fluid requirements through enteral nutrition (EN).<sup>1</sup> The etiology of neonatal and pediatric IF varies from short bowel syndrome (SBS) due to extensive bowel resection to severe primary dysmotility disorders and rare enteropathies.<sup>2</sup> During the last decade, the prognosis of pediatric IF has greatly improved.<sup>3,4</sup> Still, these patients face many risk factors for developmental delay during their illness including the underlying disease, multiple operations, repeated general anesthesia, infections and prolonged hospitalization. Besides, development may also be further compromised due to inadequate nutrition.<sup>6,8-10</sup> While slow growth interferes with normal neurological development, prolonged parenteral nutrition (PN) is a recognized risk factor for white matter injuries among preterm babies.<sup>8</sup> Prematurity and low birth weight are well-known risk factors of necrotizing enterocolitis (NEC), which has been repeatedly shown to impair neurological outcomes.<sup>6,11-14</sup> Nevertheless, also term children with SBS due to mid-gut volvulus, gastroschisis, small bowel atresia or Hirschprung's disease are subject to prolonged hospitalization, multiple laparotomies and general anesthesia during the vulnerable neonatal period. Major surgeries during the first months of life have been associated with developmental delay, whereas the role of general anesthesia on cognitive outcome remains debated.<sup>15-20</sup> Furthermore, long hospitalization interferes with normal child-parent interaction.<sup>21,22</sup> Children with neonatal and pediatric onset dysmotility syndromes and congenital enteropathies are more likely to be born full term and are hence spared from the risks a prematurity brings. However, they are also subject to prolonged PN and hospitalization and may require early surgical treatment.<sup>23-25</sup>

Along with improved survival, the long-term neurological development of pediatric IF patients has become an important area of growing interest. Therapeutic interventions can alleviate problems associated with developmental delay.<sup>26</sup> However, there are no systematic studies published to date among pediatric patients with a history of IF investigating their developmental profile beyond infancy. In this study, we sought to assess cognitive and motor impairment among children between 3 and 16 years with a history of IF and to depict underlying risk factors associated with adverse neurodevelopmental outcomes. We expected neurodevelopmental problems to be more common among children with IF than in the normal population.

## **Materials and Methods**

### **Study setting**

We conducted this prospective cross-sectional single-center study in the Helsinki University Children's Hospital between August 2017 and April 2018. Our hospital serves as a nationwide referral center for children with IF with an intestinal transplantation program.<sup>4</sup>

### **Patients**

We invited all eligible patients with IF due to SBS, primary dysmotility disorders or enteropathies to participate. Inclusion criteria were a requirement of PN for more than 60 consecutive days at the onset of IF and, for SBS patients, less than 50% of age-adjusted small bowel remaining after surgical resection. The age requirement was from 3 to 16 years at the time of the examination.<sup>27</sup> We excluded patients with known genetic syndromes or congenital central nervous system malformations affecting neurodevelopment, patients with grade III to IV intracerebral hemorrhage during neonatal period or hydrocephalus, and patients currently hospitalized due to acute illness (Figure 1). Differences in patient characteristics between the participants and eligible non-participants were analyzed. Written informed consent was

signed by the parents of the attending children and by all children over 6 years old prior to study. Children who spoke Finnish as a second language were evaluated for their linguistic skills only when adequately mastered Finnish language was in daily use.

## Methods

We assessed the cognitive and motor skills using validated tests with established normal population reference values. Psychological testing was carried out in 2 hours with a break in between two sessions and motor testing in one-hour session. Psychological testing was conducted by one of the two study psychologists and motor testing by a certified pediatric physiotherapist. They were blinded to the patients' medical history. Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) for Children between three to six years old and Wechsler Intelligence Scale for Children (WISC-IV) between seven to sixteen years old covered Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI) and Intelligence Quotient (IQ).<sup>28, 29</sup> The scores are classified as follows: Extremely low  $\leq 69$  (SD  $\leq -2.01$ ), borderline 70–79 (SD -2.00 to -1.34), low average 80–89 (SD -1.33 to -0.68), average 90–110 (SD -0.67 to 0.67), high average 111–120 (0.68 to 1.33), very high 121–130 (1.88 to 2.0), extremely high  $\geq 131$  (SD  $\geq 2.01$ ).

Motor development was examined with the Movement Assessment Battery for Children, version 2 (Movement ABC-2 test). The examination included domains assessing manual dexterity, aiming and catching, and balance. Significant moving difficulty was considered when the test score was  $\leq 56$  ( $\leq 5^{\text{th}}$  percentile) whereas score between 57–67 (6<sup>th</sup>–16<sup>th</sup> percentile) was indicative of risk of having moving difficulty. Scores  $\geq 67$  ( $\geq 16^{\text{th}}$  percentile) were perceived as normal.

An internet-based questionnaire assessing socioeconomical status was sent to all participants. The questions covered learning difficulties of siblings and an open question about parents'

worries over child's general development. Patients' medical history was collected from patient records and our IF registry.

### **Statistical Methods**

Cognitive test results were compared to VCI, PRI and IQ score distributions of the general background population and Movement ABC-2 test percentiles were calculated.<sup>28-30</sup> To assess possible risk factors for severe cognitive impairment, we divided the patients into two groups: those who had an IQ  $\geq 66$  or were estimated to have normal or mildly impaired cognitive function and those who had an IQ  $< 66$  or had serious neurocognitive impairment.<sup>31</sup> The IQ score  $< 66$  was chosen as an indication of severe cognitive impairment as all these children need further investigations for the differential diagnosis of intellectual disability. If the IQ test result was available, that was used for the grouping. The children who were unable to complete all the neuropsychological tests were investigated for their recent clinical assessments.

In a separate analysis, we compared the IQ results of the following groups: children whose PN was started within first 45 days of life with those whose PN was started after the age of twelve months and, among children with SBS, those who had NEC with a group that had undergone surgical resection for other reasons. We also compared children who were currently on PN with those who had been rehabilitated to EN.

To assess risk factors for adverse motor development, children with abnormal motor development (Movement ABC-2 tests percentiles between 0.1 and 16) were compared to those with normal motor development (Movement ABC-2 tests percentiles  $\geq 16^{\text{th}}$  percentile). The data are presented as medians with interquartile ranges (IQR) unless stated otherwise. GraphPad Prism version 7.00 was used for statistical analysis except for multiple regression. Analyses comparing the groups described above were performed using two-tailed Mann-Whitney test. IBM SPSS version 22.0 was used to calculate multiple linear regression to test



the effect of low birth weight, number of laparotomies and length of PN on IQ scores. P value  $\leq 0.05$  was considered significant.

The Strengthening the Reporting of Observational studies in Epidemiology for cross sectional studies (STROBE) guidelines were used in the process of writing the article.

The ethical committee of Helsinki University Hospital approved this study (Study number 1881/ 2017).

## **Results**

The selection process of patients is outlined in Figure 1. All 30 patients who participated in psychological testing were included in the study. Most children (24, 80%) had developed the illness leading to intestinal failure during the neonatal period. However, there were six children whose PN was initiated after the first year of life.

Detailed patient characteristics are described in Table 1. Comparison of baseline patient characteristics between participants (n=30) and non-participants (n=10) revealed no significant differences except for greater percentage of girls among non-participants (60% vs. 20%,  $p=0.0249$ ) (Supplementary Table, Supplemental Digital Content, <http://links.lww.com/MPG/B728>).

Twenty-four (80%) patients spoke Finnish as a first language. Of the six (20%) children with Finnish as their second language four spoke Finnish in day care, in school or with one parent. Three of them underwent successful psychological testing (Figure 1).

### **Distribution of IQ, VCI and PRI scores**

The entire psychological assessment was completed by 26 patients. The distribution of VCI, PRI and IQ scores compared to normative test reference scores is shown in Figure 2. The median IQ was 78 (IQR 65–91), median VCI score 74 (IQR 60–92) and median PRI score 79 (IQR 67–91). Of all patients, 15 (56%) scored under 80, and 10 (35%) patients had an IQ

under 70 (-2 SD) compared to 7% and 2.2% respectively, in these categories in the normal population.

### **Risk factors for severe neurocognitive impairment**

To evaluate possible risk factors for severe neurocognitive impairment, children who had IQ < 66 or serious neurocognitive impairment (n=8, 27%) were compared to those who had IQ ≥ 66 or were estimated to have normal or mildly abnormal cognitive function (n=22, 73%). The children with severe neurocognitive impairment had less small bowel remaining (P=0.005), they had undergone a greater number of laparotomies (P=0.007) and general anesthesia (P=0.010), and a longer hospitalization after birth (P=0.047) than those with normal or mildly abnormal cognitive function (Table 1).

In a multiple linear regression model ( $R^2=0.577$ ,  $P<0.001$ ), IQ increased 0.9 points for each additional 100 grams in birth weight (95%CI 0.4–1.4,  $P=0.001$ ), decreased 0.25 points for each additional month on PN (95%CI 0.12–0.38,  $P<0.001$ ) and decreased 1.47 points for each additional laparotomy (95%CI 0.036–2.9,  $P=0.045$ ).

Children whose PN was started after the age of 12 months (6, 20%) had normal median IQ of 96 (86–105). Most of these children (80%) had dysmotility syndrome as a cause of IF. The difference was significant when compared to IQ of 74 (IQR 60–85) in children (24, 80%) whose PN was started during the neonatal period ( $P=0.005$ ). Within the SBS group, IQ scores were similar when NEC patients (74, IQR 60–92) were compared to other surgical etiologies (70, IQR 55–94,  $P=0.276$ ).

Children who were on PN during the time of the testing had significantly lower IQ scores (65, IQR 55–77) when compared to children who had weaned off PN (86, IQR 68–100,  $P=0.0223$ ).

### **Motor development and Movement ABC-2 test results**

Twenty-eight patients completed the Movement ABC-2 test. The median percentile was 9 (IQR 2–34). The median percentile for manual dexterity was 13 (IQR 4–28), for aiming and

catching 37 (IQR 13–50), and for balance 16 (IQR 5–50). Results of ten patients (36%) fell into low percentiles between 0.1 and 5 indicating a significant impairment in motor skills. An additional eight patients (28%) had percentiles between 9 and 16, indicating a risk of abnormal motor development. Ten (36%) patients had normal percentiles between 25 and 99.9. There were five patients who had both a significant motor impairment and a severe neurocognitive impairment.

To assess risk factors for impaired motor development, we compared children with low percentiles  $\leq 16$  with those whose motor development was normal (Table 2). An impaired motor development was associated with prematurity ( $P=0.029$ ), lower birth weight ( $P=0.024$ ), and lower IQ scores ( $P=0.020$ ).

### **Socioeconomical factors**

Parents of 23 children (77%) answered the questionnaire covering socioeconomical factors and parental concern. Parents' income or educational level or learning difficulties of first-degree relatives were not associated with neurocognitive impairment (data not shown).

### **Discussion**

Our study suggests that, among children with a history of neonatal IF, neurocognitive and motor impairment are alarmingly common even when comorbidities affecting the central nervous system (CNS) are excluded. The risk for adverse outcome is highest among neonatal SBS patients. Of the study patients, one third had IQ scores under -2 SD and half scored under -1 SD when compared to normative reference values. Difficulties in motor functions were equally common, as over one third of the patients had abnormal motor development and another third were considered at risk. The major underlying factors associated with severe cognitive impairment included shorter remaining small bowel, increased number of laparotomies and general anesthesia procedures and prolonged hospitalization after birth,

whereas difficulties in motor function associated with prematurity and low birth weight. These findings are in line with those reported recently among younger children with IF.<sup>32,33</sup> Chesley et al. studied 17 IF children at a mean age of 17 months. Four children (27%) had developmental impairment as defined by the Mental Developmental Index (MDI) under 70 ( $\leq 2.01$  SD). MDI scores between -1 SD and -2 SD were found in additional 40% of the children. In the study adverse developmental outcome associated with an increased number of surgical procedures, longer hospitalization and prematurity.<sup>33</sup> These findings are comparable to our distribution of IQ scores later in childhood, and also to our associated risk factors except for the prematurity, which seemed not to be a major factor for cognitive weakening in our study. The association of cognitive impairment with neonatal surgery has been addressed in several previous studies and is well established for NEC.<sup>6,11-14</sup> Major surgery in term and near-term neonates for other indications also carries a risk for later cognitive problems.<sup>13, 16-18,34-36</sup> In longitudinal follow-up studies, any major surgery during the neonatal period was associated with developmental delay at one and three years when compared to healthy peers.<sup>17,18</sup> Another study evaluating MRI scans within ten days after neonatal surgery found white matter abnormalities indicative of hypoxic injury in 75% of the preterm and 58% of the term babies.<sup>34</sup> The need for early surgical intervention may reflect underlying harmful systemic pathology hampering brain development during the neonatal period.<sup>34</sup> However, the surgery itself, together with the inflammatory response it provokes, may be equally destructive to the developing CNS during this vulnerable period. This is supported by our observation that children with late onset IF after 12 months of age showed no remarkable cognitive impairment. Most of them had dysmotility syndrome as a cause of IF.

Both low birth weight and poor pre- and post-natal growth are known to adversely affect cognitive performance.<sup>7,37-38</sup> The regression analysis showed the effect of low birth weight on cognitive results in our study as well. Systemic inflammation and poor nutrition during the

neonatal period affect growth and hence have a negative effect on neurological development.<sup>7</sup> IF children with more severe disease forms require longer PN, are at risk for repeat infections, and are more likely to develop nutritional deficiencies during enteral rehabilitation.<sup>10</sup> The adverse effect of prolonged PN is also shown in our study where children who continued on PN during the study period had lower IQ scores than children who had rehabilitated to EN. In group comparisons, longer duration of PN in children with severe neurocognitive impairment was also apparent, although it remained statistically insignificant.

When preterm children are compared to those born full term, IQ scores lower than average are generally reported.<sup>39,40</sup> However, in the Finnish PIPARI study extremely preterm children performed reassuringly well in cognitive tests. Compared to the IF patients of our study, the cognitive performance among the PIPARI preterm cohort was better.<sup>37</sup> Although both birth weight and prolonged parenteral nutrition were associated with cognitive impairment in our regression analysis, four out of the eight severely impaired children were born after 36 gestation weeks and only two before 28 weeks, indicating that prematurity was not the major culprit.

Movement difficulties and risk for motor development delay are associated with extreme prematurity and low birth weight, as demonstrated also in our study.<sup>41,42</sup> In previous studies, major surgery has also been associated with motor delay. This delay in motor function might be reversible, although previous studies on the matter have presented controversial results.<sup>16-17,43</sup> In our study, patients' Movement ABC percentiles were similar in all age groups.

Although the number of surgeries was not associated with adverse motor development in this study, in a previous study by So et al. with 33 children with IF at the corrected age of 12 to 15 months it was one of the associated risk factors. However, comparable to our study, the adverse neuromotor development mainly associated with prematurity and low birth weight.

Other risk factors included co-morbidities of the CNS, hyperbilirubinemia, NEC, and longer intensive care stay.<sup>32</sup>

There are limitations to this study. As pediatric IF is a rare disease, the number of patients examined was too small to allow for definitive analysis of underlying factors. Also, there is possible bias, as 25% of the eligible patients did not attend the study. We could not analyze the socioeconomical factors in the non-attending group, which also had a greater percentage of girls compared to the attending group. As it is possible that non-native Finnish speakers could receive lower scores in verbal tests, the patients who were suspected of having linguistic challenges were excluded from the VCI and IQ score analyses, further reducing the number of patients included in the analyses

However, this study reached a representative portion of our patients. The strengths of this study include that our center follows a strict follow-up protocol, ensuring that all the children receive equal and standardized care. Most importantly, this study brings new information about the neurological development of children with a history of IF.

In our hospital, children born before 30 weeks GA or weighing under 1,500 grams at birth are routinely checked for neurological development at a pediatric neurologist appointment, whereas children born at later gestational age are referred to a neurologist only when neurodevelopmental problems are suspected. During this study, children with IF were found to have both severe and milder neurocognitive and motor impairments that had gone unnoticed by general health practitioners and pediatricians even though parental worry and problems at school or preschool had arisen. It is possible that due to somatic problems, developmental issues are overlooked. We recommend early neurological follow-up for all children with a history of IF. As these children encounter different problems in several areas of development, their rehabilitation, e.g. physiotherapy, occupational therapy and speech therapy, is always individualized. All interventions should have measurable goals mutually

agreed with the child and caregivers, and the intervention should apply methods which activate and motivate the child in their natural environment (e.g. home, day care, school).

## **Conclusion**

Children with neonatal IF, and especially with neonatal SBS, are at significant risk of neurocognitive and motor impairment. It is likely that developmental problems are underdiagnosed in this patient group. Timely intervention can both improve neurodevelopmental outcomes and alleviate the associated problems.<sup>26</sup> We strongly recommend systematic longitudinal neurological assessment of all children with a history of IF.

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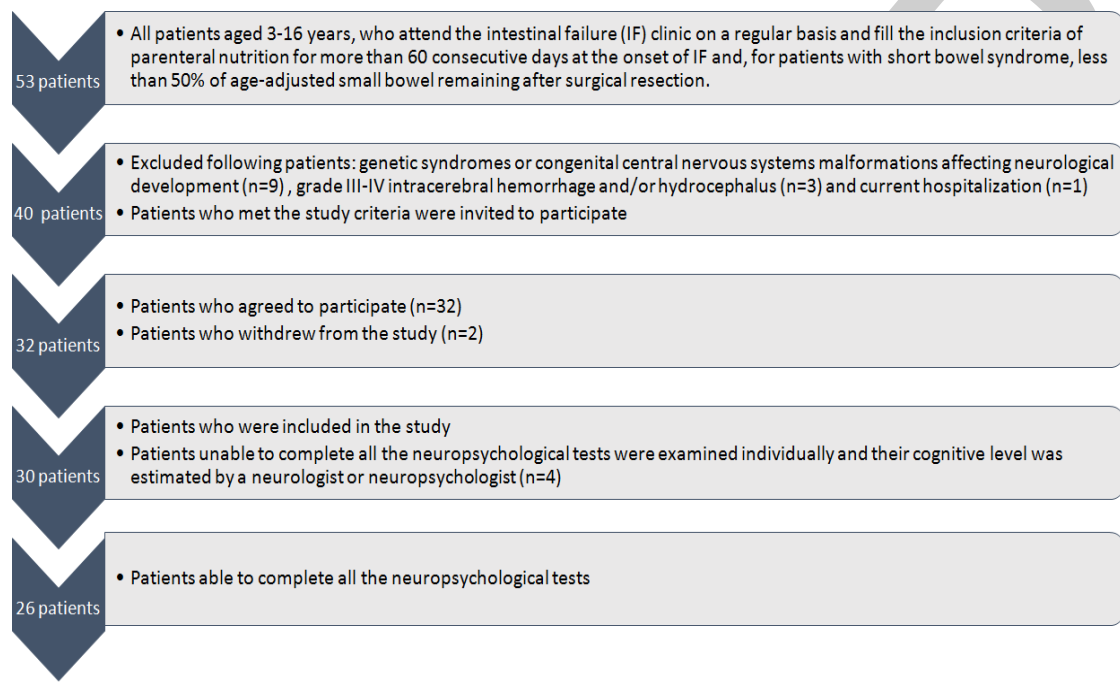
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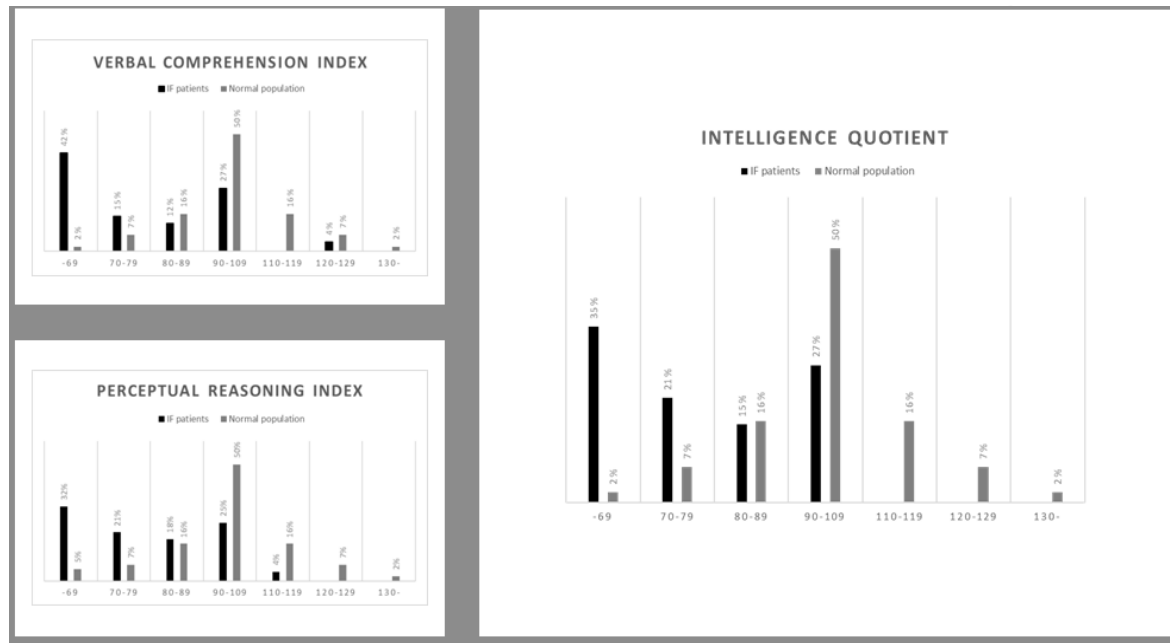
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**Figure 1.** Flow chart of the patient selection process.

<sup>a</sup> Reasons for not finishing the cognitive tests were severe neurocognitive impairment (n=1), inadequate language skills (n=1) and inadequate cooperation (n=2). The neurocognitive development of the three latter patients was estimated to be mildly abnormal (n=1) or within normal limits (n=2).



**Figure 2.** VCI, PRI and IQ distribution of pediatric IF patients (n=26) completing the neurocognitive assessment study, compared with the score distribution in general population. The scores are described as follows: Extremely low  $\leq 69$ , very low 70-79, low average 80-89, average 90-110, high average 111-120, very high 121-130, extremely high  $\geq 131$ .



**Table 1.** Patient characteristic of all patients with intestinal failure and comparison of patients with normal or mildly impaired cognition and severe cognitive impairment

Characteristics	All study patients (n=30)	Patients with normal or mildly impaired cognition <sup>a</sup> (n=22)	Patients with severe cognitive impairment <sup>b</sup> (n=8)	P-value <sup>c</sup>
Age, years (IQR)	7.5 (5.2-10.4)	6.0 (3.8-8.3)	10.4 (6.0-13.2)	0.058
Male, n (%)	24 (80%)	18 (82%)	6 (75%)	>0.999
IF etiology, SBS/dysmotility/other, n	23 / 5 / 2	15/ 5 / 2	8 / 0 / 0	0.143
Etiology for SBS, NEC/another <sup>d</sup> , n	11 / 12	8 / 7	3 / 5	0.667
GA at birth, weeks (IQR)	35 (28-38)	36 (27-38)	30 (28-38)	0.555
Children born $\leq$ 28 weeks, n (%)	8 (27%)	6 (27%)	2 (25%)	>0.999
BW, grams (IQR)	2238 (1014-3288)	2480 (1088-3378)	1225 (823-3076)	0.339
Children with BW $\leq$ 1500 g, n (%)	13 (43%)	8 (36%)	5 (63%)	0.242
Duration of PN, months (IQR)	13 (5-37)	11 (4-24)	43 (8-131)	0.069
Short bowel percentage, % (IQR) <sup>e</sup>	30 (21-72)	43 (25-100)	20 (12-25)	<b>0.005</b>
General anesthesia, n (IQR)	9 (8-14)	8 (7-11)	14 (12-16)	<b>0.010</b>
Age at first general anesthesia, months (IQR)	0.2 (0-1)	0.4 (0.1-0.5)	0.2 (0.0-0.4)	0.127
Laparotomies, n (IQR)	4 (2-5)	3 (2-5)	6 (4-11)	<b>0.007</b>
Duration of hospitalization after birth, months (IQR)	4.8 (1.2-10)	3.8 (0.0-9.3)	9.5 (5.0-13)	<b>0.047</b>
Blood culture positive septicemia, n (IQR)	1 (1-2)	1 (0-2)	2 (1-3)	0.315

<sup>a</sup> Defined as IQ < 66 (n=7) or diagnosed with serious neurocognitive impairment by neurologist (n=1)

<sup>b</sup> Defined as IQ  $\geq$  66 (n=19) or estimated to have normal or mildly impaired cognitive function by psychologist (n=3)

<sup>c</sup> p-value is calculated using two-tailed Mann-Whitney test for comparisons between patient groups of normal or mildly abnormal and severely abnormal neurodevelopment and significant differences have been bolded.

<sup>d</sup> Midgut Volvulus (n=5), small bowel atresia (n=2), gastroschisis in (n=2) and small bowel strangulation (n=1), Hirschsprung's disease (n=1) and malrotation (n=1)

<sup>e</sup> Struijs MC, Diamond IR, de Silva N, et al. Establishing norms for intestinal length in children. J Pediatr Surg. 2009; 44:933-938.

Abbreviations: birth weight (BW), gestational age (GA), intelligence quotient (IQ), interquartile ranges (IQR), intestinal failure (IF), necrotizing enterocolitis (NEC) parenteral nutrition (PN), short bowel syndrome (SBS), standard deviation (SD)

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**Table 2.** Comparison of pediatric intestinal failure patients with normal and abnormal motor development according to Movement assessment battery for Children, 2<sup>nd</sup> edition, test results.

Characteristics	Normal motor development (n=10) <sup>a</sup>	Abnormal motor development (n=18) <sup>b</sup>	p-value <sup>c</sup>
Age, years (IQR)	6.1 (3.7-10.1)	8.0 (7.2-11.6)	0.058
Gender, male (%)	7 (70%)	15 (83%)	0.635
IF etiology, SBS /dysmotility, n	7 / 3	16 / 2	0.315
GA at birth, weeks (IQR)	38 (24-36)	30 (34-39)	<b>0.029</b>
Children born $\leq$ 28 weeks, n (%)	1 (10%)	7 (39%)	0.194
BW, grams (IQR)	3024 (2103-3400)	1225 (743-2745)	<b>0.024</b>
Children with BW $\leq$ 1500 g, n (%)	2 (20%)	12 (67%)	<b>0.046</b>
Duration of PN, months (IQR)	10 (4-15)	15 (6.4-40)	0.171
Short bowel percentage, % (IQR) <sup>d</sup>	35 (22-100)	27 (5-44)	0.259
General anesthesia, n (IQR)	9 (7-11)	11 (8-16)	0.228
Laparotomies, n (IQR)	3 (3-5)	4 (2-5)	0.136
Duration of hospitalization after birth, months (IQR)	1.8 (0-10)	5.5 (3.4-13)	0.072
Blood culture positive septicemia, n (IQR)	1 (0-2)	2 (1-3)	0.052
IQ, score (IQR)	88 (75-103)	74 (55-87)	<b>0.020</b>

<sup>a</sup> Indicated as MABC-2 test percentiles between 25 to 99.9 and scores  $>67$  points.

<sup>b</sup> Indicated as MABC-2 tests percentiles between 0.1 to 16 and test scores  $\leq 67$  points

<sup>c</sup> p-value is calculated using two-tailed Mann-Whitney test for comparisons between patient groups of normal and abnormal motor development and significant differences have been bolded.

<sup>d</sup> Struijs MC, Diamond IR, de Silva N, et al. Establishing norms for intestinal length in children. J Pediatr Surg. 2009; 44:933-938.

Abbreviations: birth weight (BW), gestational age (GA), intelligence quotient (IQ), interquartile ranges (IQR), intestinal failure (IF), Movement assessment battery for Children, 2<sup>nd</sup> edition (MABC-2), parenteral nutrition (PN), short bowel syndrome (SBS), standard deviation (SD)